

EXHIBIT 41

Available online at www.sciencedirect.com**Journal of Hospital Infection**journal homepage: www.elsevierhealth.com/journals/jhin**Review****Infection control hazards associated with the use of forced-air warming in operating theatres****A.M. Wood^a, C. Moss^a, A. Keenan^b, M.R. Reed^a, D.J. Leaper^{c,*}**^a Northumbria Healthcare NHS Foundation Trust, Ashington, UK^b Royal Infirmary of Edinburgh, Edinburgh, UK^c Huddersfield University, Huddersfield, UK**ARTICLE INFO****Article history:**

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SUMMARY

A review is presented of the published experimental and clinical research into the infection control hazards of using forced air-warming (FAW) in operating theatres to prevent inadvertent hypothermia. This evidence has been reviewed with emphasis on the use of ultra-clean ventilation, any interaction it has with different types of patient warming (and FAW in particular), and any related increased risk of surgical site infection (SSI). We conclude that FAW does contaminate ultra-clean air ventilation; however, there appears to be no definite link to an increased risk of SSI based on current research. Nevertheless, whereas this remains unproven, we recommend that surgeons should at least consider alternative patient-warming systems in areas where contamination of the operative field may be critical. Although this is not a systematic review of acceptable randomized controlled clinical trials, which do not exist, it does identify that there is a need for definitive research in this field.

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Introduction

Perioperative patient warming has been shown to have clinical benefits across a wide range of surgical procedures, and the current market device leader, forced-air warming (FAW), has also been demonstrated to reduce surgical site infection (SSI) rates after colorectal surgery.^{1–5} However, its use during orthopaedic implant surgery to prevent SSIs is unproven and the combined use of FAW and ultra-clean ventilation (UCV) flow is controversial. The theories and indications for implementation of each these two systems, which both affect air circulation in the operating theatre, and how they interact with

particular emphasis on SSIs after orthopaedic implant surgery, is reviewed.

Ultra-clean ventilation

The importance of reducing bacterial colony-forming units (cfu) in surgical wounds was demonstrated in the seminal papers of Charnley and Eftekhar, and of Lidwell, who concluded that it only requires 10 cfu to cause a deep SSI after joint replacement surgery.^{6,7} Charnley hypothesized that the 'surgical implant might provide a nidus for the growth of airborne bacteria which ordinarily were accepted as being non-pathogenic'.⁸ This hypothesis has been expanded and it is now accepted that implanted biomaterials can potentiate bacterial growth on their surface, through formation of biofilms, and that opportunistic organisms can become virulent pathogens in the presence of implants. It has been established that the most

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important factor in the bacterial 'race for the surface' is the initial bacterial load.^{9,10} In the early 1970s Charnley advocated the use of clean air to reduce the incidence of infection in orthopaedic surgery, and instigation of this intervention has been acknowledged as being critical in preventing orthopaedic SSIs and joint infections.^{6,7}

Ultra-clean ventilation works by reducing the quantity of airborne bacteria in the operating theatre and most importantly at the wound site. For this reason microbiological air-sampling adjacent to the instrument trolleys is recommended.¹¹ This is achieved by the constant delivery of highly filtered ultra-clean air with a downward uniform velocity (0.3–0.5 ms).^{12,13} Specifications vary but this can result in >500 air changes per hour.¹⁴ UCV flow has been shown to reduce the airborne bacterial count from 5.4/ft³ in a standard operating theatre to 0.45/ft³ in a UCV flow theatre.¹⁴ This is achieved by high-flow air passing through a high-efficiency particulate air (HEPA) filter.¹⁵ These filters remove 99.97% of all particles that are >0.3 µm in size. Finally, air can be streamed horizontally or vertically but it has been demonstrated that streaming in a vertical pattern is best.^{7,16}

The performance of UCV depends critically on airflow volumes, proper temperature gradients, and lack of turbulence.¹³ It has also been shown that local turbulence, even that caused by movement of the surgeons' heads, can disrupt the UCV flow within an enclosure, thereby increasing the amount of cfu in the operating field.¹⁷ The use of ultra-clean air has become standard practice in the UK following the report by Lidwell *et al.* on 8000 operations, which demonstrated that ultra-clean air contributed to a significant reduction of infection after joint replacement (odds ratio: 0.5).⁵ Despite its popularity in the UK, UCV flow is not used universally for implant surgery around the developed world.

Benefits of avoiding perioperative hypothermia

Hypothermia is defined as a core temperature below 36°C and the reasons leading to hypothermia in the perioperative period are multifactorial.¹⁸ In an operating theatre kept at 21°C, an anaesthetized patient not covered with surgical drapes can lose up to 50 kcal of body heat per hour in a plenum-ventilated theatre suite in which there are 15–20 air changes per hour. This may increase by 400 kcal/h in UCV theatres.^{19–21} These losses of body heat are compounded by heat loss from wound lavage, intravenous infusion and respiratory heat exchange.^{22,23}

Preventing inadvertent perioperative hypothermia decreases the duration of surgery, reduces morbidity and mortality, incidence of postoperative pressure ulcers, length of stay in intensive care and total hospital stay.^{1,24–26} It has also been associated with a reduced requirement for mechanical ventilation, and blood transfusion.¹ This latter effect is believed to be secondary to reduced efficiency of the coagulation cascade in hypothermic patients which can lead to an increased requirement for blood transfusion.^{27–30} Maintaining normothermia has also been shown to decrease the rate of myocardial infarction and dysrhythmias, which is probably related to the surge in noradrenaline and vasoconstriction which may be caused by hypothermia.¹ Hypothermia leads to a decreased rate of drug metabolism.³¹ Even mildly hypothermic patients have an increased duration of circulating intravenous neuromuscular drugs and increased toxicity of other drugs.³²

Consequently postoperative hypothermia can lead to a delay in recovery from anaesthesia.³³

Hypothermia can cause relative hypoxia of tissues as a result of peripheral vasoconstriction, and in animal models hypoxia has been shown to reduce resistance to infection with *Staphylococcus aureus*, particularly when partial pressures are <40 mmHg.³⁴ This is believed to be due to the oxidative properties of phagocytes in killing bacteria.³⁵ The vasoconstrictive effect of hypothermia is also believed to reduce the development of strength in the healing wound by decreasing the amount of collagen that is laid down.^{4,36} Hypothermia has also been reported to be associated with an increased risk of wound infection.³⁷ Melling *et al.* randomized 421 patients into a non-warmed group or one of two pre-warmed groups (local and systemic) and demonstrated a statistically significant, almost three-fold, reduction of SSI after clean (breast, varicose vein, or hernia) elective surgery in the pre-warmed groups.⁵ Although often quoted as doing so, this study did not consider the effect of intraoperative warming. Only one study, involving colorectal surgery (by definition clean-contaminated or contaminated), has demonstrated that FAW reduces the rate of SSI.^{24,38,39} The authors of this study reported a three-fold reduction in SSI rates in patients who were warmed when compared to patients who were not warmed during surgery.²⁴ Whereas these researchers did use FAW to warm patients during surgery in the intervention group, a confounding factor was that they also used an average of 3 L of warmed fluid in the intervention group compared to the control group, in which fluid was not warmed.

Warming methods

Intraoperative warming systems fall into three broad categories: FAW (Figure 1), resistive polymer fabric warming (Figure 2), and circulatory warming systems using a closed fluid circuit to maintain a given temperature.

Since the 1990s, FAW has been the market device leader for perioperative warming. In general, these devices consist of a warming unit or heat generator combined with a blower to help circulate filtered air. The warm air flows through a connecting hose into blankets made of paper or plastic, which have multiple different compartments through which the air moves. The warm air then exits the blankets through holes over the patient's skin and heats the patient by convection.⁴⁰ These systems are regulated by a number of temperature control systems to sense the heat of the air being pumped through and to prevent overheating or burning of the patient.⁴¹ This system is limited by the surface area available to be covered. Each blower manages one blanket; thus, some surgical sites may require two systems in order to adequately cover a large percentage of body surface area. Other limitations include: the noise of the system, the cost of consumables – although no robust analysis between the two groups has been performed – and the potential risk of contamination from the pump and air-hose system.⁴²

Resistive heat warming is based on resistive polymer technology.⁴³ The system is safe as it uses low-voltage DC currents passing through a semiconductive polymer fibre fabric with temperatures safely maintained by a central computer. The system can control separate fields independently, whereby large non-operative sections of the body can be covered by blankets and/or an underlying mattress allowing a large

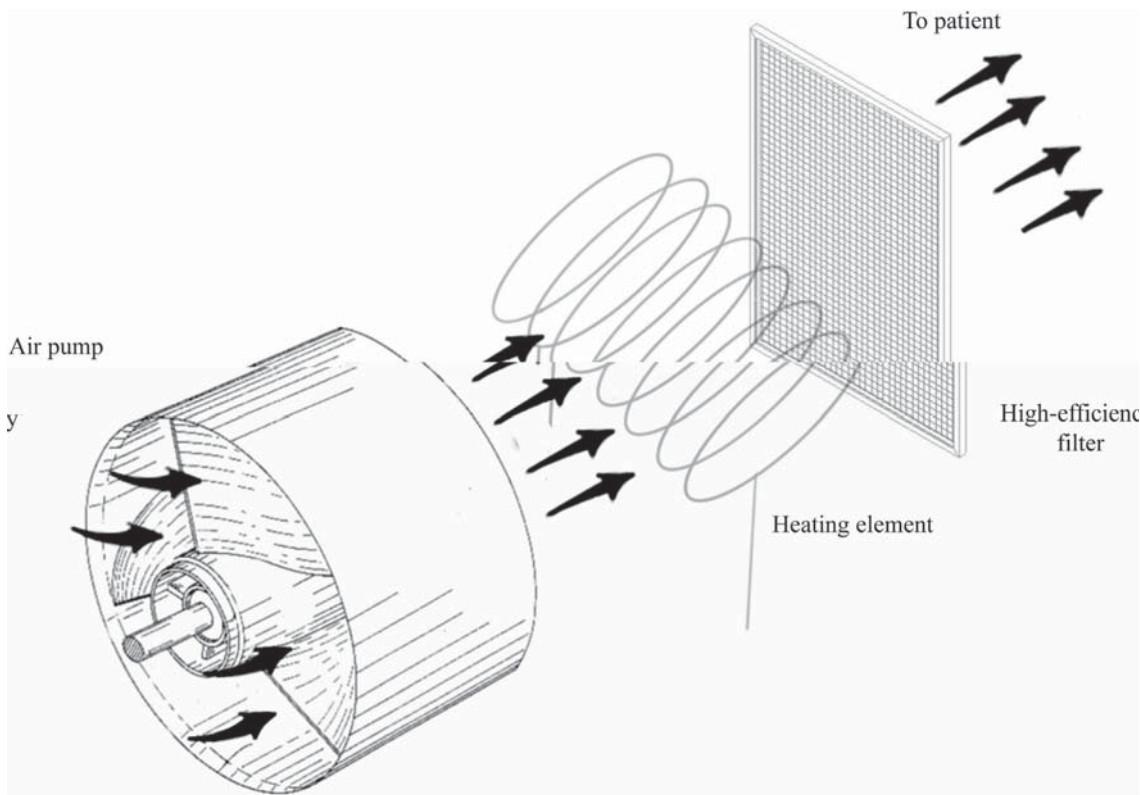


Figure 1. Generation of forced-air warming.

percentage area of the body to be warmed during any operation.^{44,45} An advantage of this system is its re-usability, and there are no moving parts, which makes the system noiseless in use. Unlike FAW systems, they do not require a disposable blanket component being replaced between patients. Having no disposable component gives resistive heat warming an unproven cost advantage but mattresses and over-blankets require careful decontamination of possible pathogens between patients. Less heat is transferred to the operating room

and staff, making it a more favourable environment in which to work.⁴⁶ Unlike FAW the blanket itself is less flexible, so it may not be directly adjacent to the patient's skin.⁴⁷ Current evidence suggests that there is little difference between FAW and resistive technologies in terms of preventing hypothermia.^{48,49}

Circulatory devices such as water mattresses and water blankets are rarely used and have limited efficacy in the operative setting.^{43,50} These mattresses have been associated with 'pressure heat necrosis' due to tissues being compressed

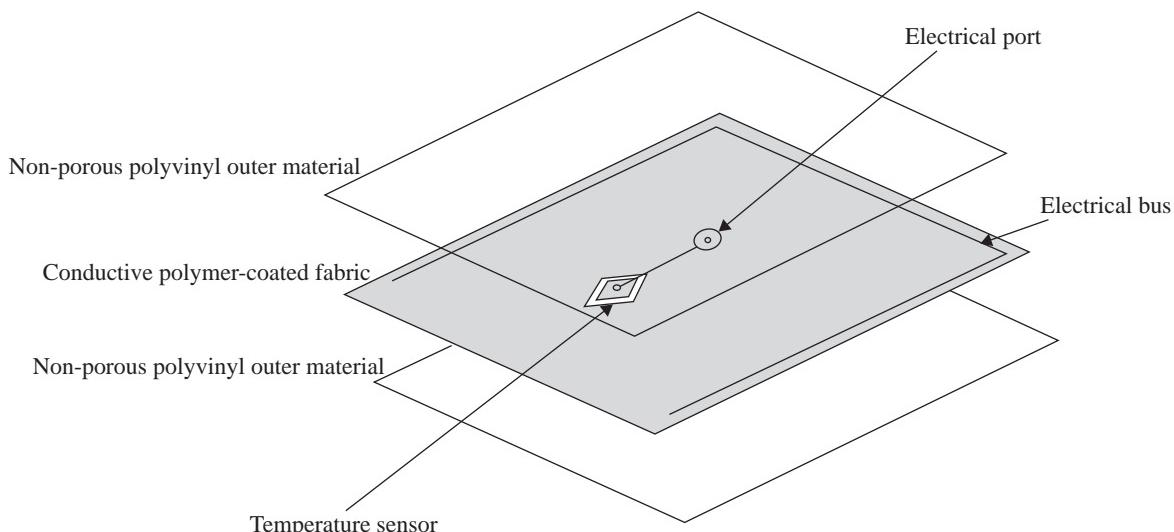


Figure 2. Generation of conductive warming.

by the patient's weight and excessive heat transfer.⁴⁸ It is also possible to use radiant heat from light sources. This is most frequently used in paediatric surgery; however, it has been trialled in cardiac patients, where rewarming times were similar to FAW. Nevertheless these systems are not as comfortable for the staff, as they heat the whole area and not just the patients. As these systems are not in frequent use for adult patients we have not concentrated on them.⁵¹

External warming systems are not the only way to avoid hypothermia during surgery. Warmed intravenous fluid and lavage, and endotracheal warming systems may be used to aid temperature regulation in the anaesthetized patient.

The National Institute for Health and Care Excellence (NICE) guidelines state that any operation lasting longer than 30 min should be accompanied with active warming of the patient using FAW or a conductive resistive polymer, fabric warming system.^{18,52} High-risk patients should be warmed during all operations.¹⁸ Avoidance of hypothermia should optimally begin on the ward, and continue through the operative procedure and recovery room, and back to the ward.

Current concerns about infection control and forced-air warming

There has been significant debate about the safety of FAW, and no studies have shown a reduction in SSI by the use of intraoperative FAW except in elective colorectal surgery.^{4,13,53} In implant surgery even minor contamination of the operative field could be catastrophic, and concerns about this focus on two areas: disruption of clean air through thermal eddies, and direct contamination of air that blows from the use of FAW blowers.

Disruption of clean air through thermal eddies

It has been hypothesized that FAW devices could affect UCV flow to negate or overturn its benefits and that the combination of different airflows could be a risk factor that may increase SSIs after arthroplasty and spinal surgery, although there could be many potential disruptions to laminar air flow in theatre.¹³ Air from FAW blowers is >20°C warmer than the ambient theatre temperature as the air from FAW blowers is heated to 43°C, which decreases before it contacts the patient.⁵⁴ In addition, excess heat is generated with these devices, typically using 1 kW, compared with only 200 W for other techniques. Both factors lead to temperature gradients which cause eddies and impede the downward laminar air flow. This in turn can lead to increased contamination at the surgical site.^{55,56}

Two research groups have used neutrally buoyant air/helium bubbles to track the movement of air when using forced air and alternative warming systems. McGovern *et al.* randomized FAW and RHW and demonstrated that significantly more unclean air moved from outside of the UCV area into the simulated surgical site of knee replacement surgery using FAW, when compared with warming using resistive polymer fabric over-blankets.¹³ A further study demonstrated that in simulated spinal surgery, air from the floor level was transported up into the site of the surgical 'wound' as a result of the FAW system.^{13,57} These findings were supported in another paper on the effects of excess heat on the movement of bubbles in UCV flow.⁵⁷ These authors demonstrated that significant convection currents formed, due to the excess heat, and that the bubbles

moved from unsterile to sterile areas. Legg *et al.* demonstrated that waste heat from the FAW blankets also created a temperature gradient because of convection currents (Figure 3), which were formed and rose against the laminar flow, and Moretti *et al.* found an increased bacterial load at the surgical site when FAW was used.^{41,58} This increased the particle concentration at the surgical site 1000-fold, when compared to controls, by drawing particles from below the surgical table to the surgical site. Other studies have also concluded that FAW generates convection current activity in the vicinity of the surgical site of the operative field.⁵⁹ The clinical concern raised by these studies is that these currents may disrupt ventilation airflows intended to clear airborne contaminants from the surgical site.¹⁴

The effect of excess heat produced by different warming systems has been analysed and FAW was found to produce the highest amount of excess heat when compared with other warming systems.⁵⁶ In this study, pockets of hot air were found above the operating site, which is against the flow of the UCV flow, and these authors have suggested that this indicates a significant disruption to the unidirectional nature of UCV flow. Again, this study could not make any conclusions about whether these changes would be a direct infection risk but they identified that there may be ways to mitigate this potential risk by channelling the warm air out of the UCV flow.⁵⁶

Other researchers have studied particle counts over operating sites in UCV flow comparing no warming, FAW, and radiant warming.⁵⁹ They found a highly statistically significant increase in the number of particles of all sizes tested in the FAW group compared to other groups (Figure 4). The disadvantage of this study is that it is not possible to see where these increased particles came from, whether they came from the floor, or from the warmer used in the study, and again it is not possible to determine whether this would lead to an increased SSI rate.⁵⁹ However, the same authors considered potentially contaminated smoke particles being drawn up from below the operating table and found that the convection currents increased the particle concentration at the surgical site 1000-fold. This use of smoke particles, with the application of FAW, has also been studied around the operating site. In a further study, the authors state that there was no clinical or statistically significant increase in particles when FAW was turned on, although they illustrated that there was a trend towards more particles when FAW was turned on rather than off. In some of the graphs there appears to be an almost 10-fold increase in particles. The authors also felt that the UCV flow still reduced the particle count to within the limits of their self-defined standard; we have summarized the major papers quoted in Table I.⁶⁰

Direct contamination of air that blows from the forced-air machines

When considering the FAW blowers themselves there are concerns about their filtration efficiency and bacterial growth in their air-path surfaces.^{52,61} The most recent study of this, using the most popular current model, demonstrated a filtration efficiency of only 63.8%, which was assessed as the fraction of 0.3–5.0 µm captured by the intake filter, and that all the machines had micro-organisms on their internal air paths – beyond the filter.⁶² Of these machines, 74% grew coagulase-negative staphylococci, which are the commonest pathogen

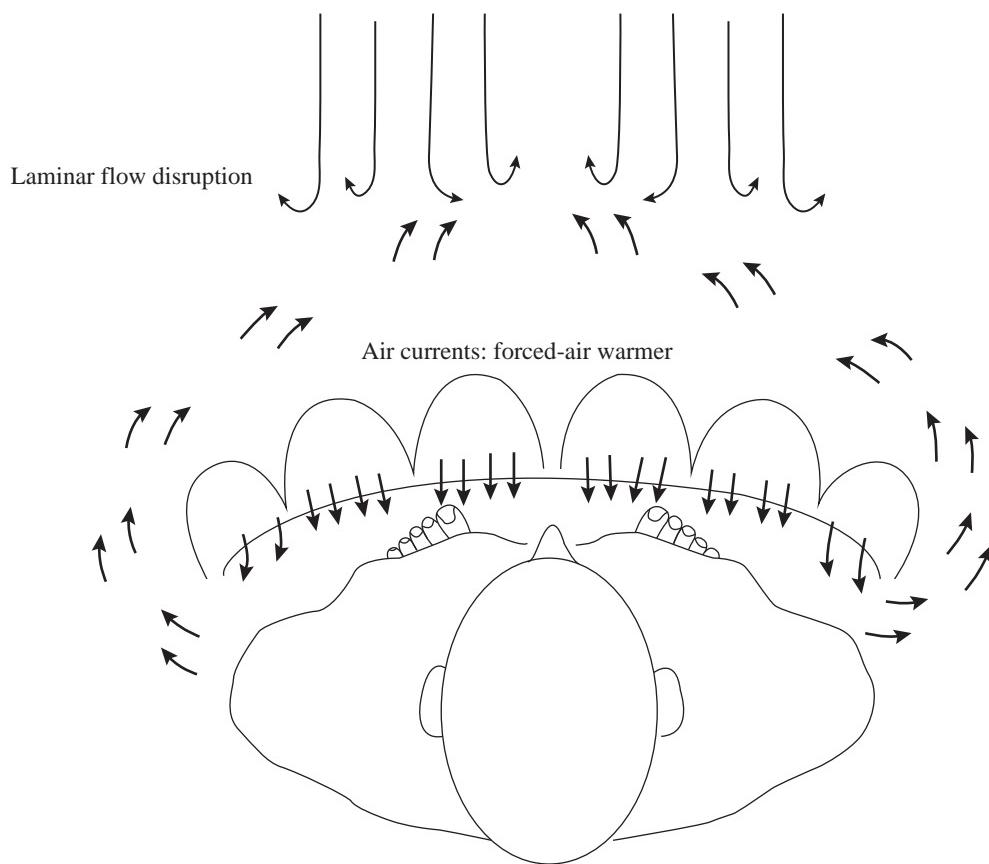


Figure 3. Potential effects on laminar flow with forced-air warming.

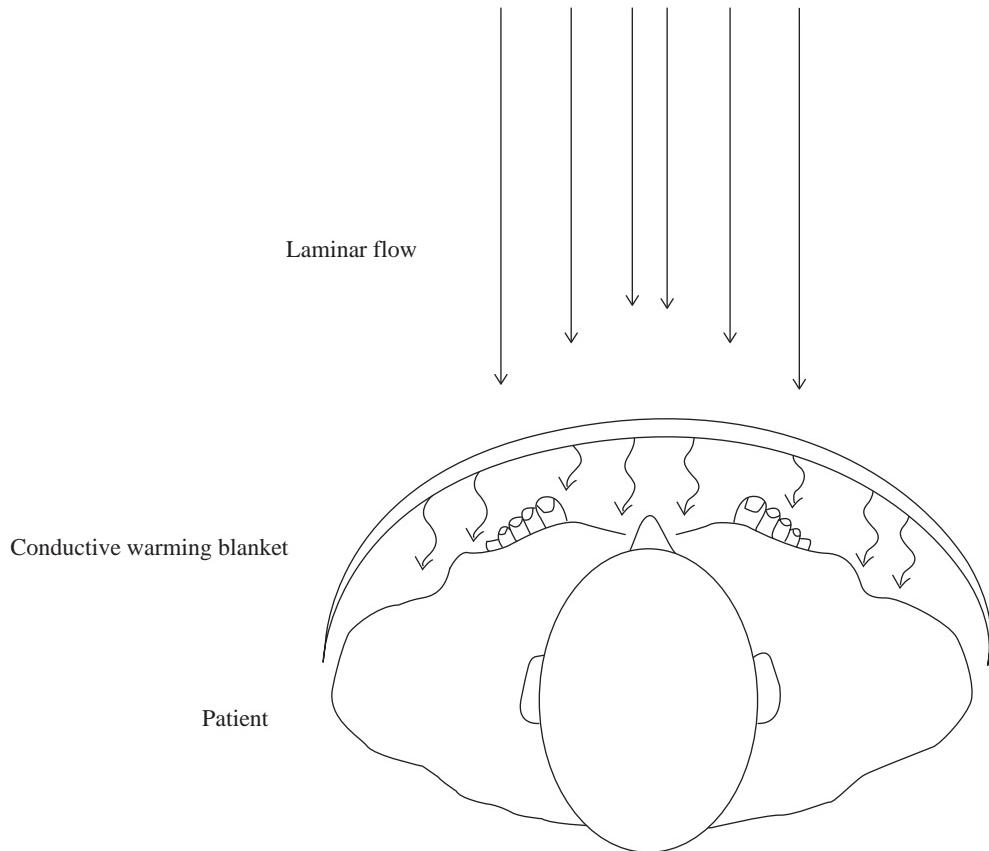


Figure 4. A conductive system does not affect laminar flow.

Table I

Summary of ten important papers regarding the use of forced-air warming (FAW) in operating theatres

Reference	Title	Study type	Outcome measure	Findings
McGovern et al. ¹³	Forced-air warming and ultra-clean ventilation do not mix: an investigation of systems theatre ventilation, patient warming and joint replacement infection in orthopaedics	Retrospective review between two warming	Deep joint infection	Significant increase in deep joint infections when FAW used
Albrecht et al. ⁵³	Forced-air warming: a source of airborne contamination in the operating room?	Modelling of airborne contamination	Particulate counts	Significant percentage of FAW blowers with positive microbial cultures were emitting internally generated airborne contamination
Kurz et al. ⁴	Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization	Prospective randomized double-blind protocol into the affects of warming in colorectal surgery	Wounds containing culture-positive pus were considered infected	Hypothermia was more likely to be associated with surgical wound infection than normothermia in colorectal patients
Chow and Yang ⁵⁵	Ventilation performance in the operating theatre	Review of research	Not applicable	Not applicable
Darsai et al. ⁵⁶	Effect of forced air warming on the performance of operating theatre laminar flow ventilation	Modelling of temperature differences using FAW and conductive blankets	Air temperature differences	Temperature differences were significantly elevated over the surgical site with a concern that this may generate convection current activity and that these currents may disrupt ventilation airflows
Belani et al. ⁵⁷	Patient warming excess heat: the effects on orthopaedic operating room ventilation performance	Modelling using neutral, buoyant, detergent bubbles	Number of bubbles over surgical site	Excess heat from FAW resulted in disruption of ventilation over the surgical site when FAW was used but not when conductive patient warming was used
Moretti et al. ⁴¹	Active warming systems to maintain perioperative normothermia in hip replacement surgery: a therapeutic aid or a vector of infection?	Level of bacterial contamination during arthroplasty with and without FAW	Level of bacterial contamination in the air during surgery	In 30 patients during six months there was no later manifestation of nosocomial infection
Legg et al. ⁵⁹	Do forced air patient-warming devices disrupt unidirectional downward airflow?	Modelling of surgical site, measuring particles and temperature	The number of particles over the surgical site and temperature increases	FAW increases the number of particles and temperatures when compared to radiant warming, raising concerns about bacterial contamination
Sessler et al. ⁶⁰	Forced air warming does not worsen air quality in laminar flow operating rooms	Modelling of tracer particles with FAW on, off, and set to high heat	Reduction of background particle count over putative surgical incision	No decrement in laminar flow performance when FAW was used
Legg and Hamer ⁵⁸	Forced-air patient warming blankets disrupt unidirectional airflow	Modelling of smoke particles over a total knee replacement	The number of particles over the operating site	Convection currents increased the particle concentration 1000-fold for FAW when compared to radiant warming by drawing particles from below the operating table

found in infected joint replacements. They also identified that 96% of blowers emitted significant levels of contaminants out of the hose end which was not attached to a blanket. The authors concluded that FAW devices should be fitted with HEPA filters to reduce the risk of contamination.⁶² This concern is reinforced by case reports in which *Acinetobacter baumannii* has been found in the dust filters of FAW systems after outbreaks of this resistant organism. Whereas Bernards *et al.*'s study was performed in an intensive care environment, and other machines were also identified as having contamination with the same species, the report does highlight that there should be a low threshold to investigate FAW devices as a potential source or factor in the spread of bacteria.⁶³ The importance of regular maintenance and cleaning, in order to reduce the likelihood of FAW devices contributing to any infections, is also highlighted, although FAW manufacturers do not currently provide a method to decontaminate the inside of the hose or blower, and in a number of cases the intake filters are not HEPA-rated.^{53,63}

In contrast, there are other studies suggesting that FAW systems may not present a real risk of nosocomial infection. In one study it was found that the increased bacterial load, seen when using forced-air ventilation, was comparable to the amount of bacteria that were present when the patient was placed on the operating table.⁵⁸ Whereas this conclusion may be correct, the study does confirm that FAW may increase the concentration of bacteria at some stages during an operation, compared with operations in which FAW is not used. This finding is supported by other studies, which have demonstrated potentially pathological organisms in FAW blower systems with other studies demonstrating a small increase in cfu in ultra-clean air theatres.^{64–66} However, these findings have not been demonstrated in other studies including vascular surgery and simulated surgery.^{67–69}

Does forced-air warming affect SSI rates in implant surgery?

Two clinical studies have addressed this issue. The first studied infection rates during a change of warming system in 1437 patients undergoing primary hip replacement.¹³ A significant increase in deep joint infection, demonstrated by a more than three-fold infection odds ratio (3.8; $P = 0.024$), was identified when FAW was used compared with conductive resistive polymer fabric warming. The authors conceded that theirs was an opportunistic study in which there was a change in practice, and may have been affected by other infection prevention measures instituted by their hospital. Again, while acknowledging that there was a small study sample size ($n = 30$), Moretti *et al.* identified that there was an increased bacterial load when FAW was used, but their study showed no increase in SSIs.⁵⁸ Although this statement is currently probably correct, the evidence surrounding the effects of FAW on UCV flow, with the increased particle counts seen during its use, supports the need for a randomized controlled clinical study.^{41,59}

Conclusion

The benefits of maintaining normothermia during the peri-operative period are without doubt. Many studies suggest that disruption of UCV air flow by FAW is significant but the effect on

SSI rates in implant surgery has yet to be determined by robust level 1 evidence.⁷⁰ We recommend consideration of the use of alternative patient warming devices when performing orthopaedic hip and knee implant surgery until a definitive trial can be performed, but that some caution in condemning FAW should be observed.

Conflict of interest statement

D.J.L. has had paid consultant advisory roles with Inditherm, Augustine and Arizant (now MMM) in the past, but has held no affiliation, professional, intellectual, or personal, with any of these companies for more than 5 years. M.R.R.'s institution has received funding for research from Augustine Biomedical more than three years ago.

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